CAROTENOIDS

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Chemistry, Sources and Physiology

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Chemistry

Structure

Most carotenoids are 40-carbon isoprenoid compounds called tetraterpenes. Isoprenoids are formed from the basic five-carbon building block, isoprene (**Figure 1**). In nature, carotenoids are synthesized through the stepwise addition of isopentenyl diphosphate (IPP) units to dimethylallyl diphosphate (DMAPP) to form the 20-carbon precursor geranylgeranyl diphosphate (GGPP). Two molecules of GGPP are combined to form the first carotenoid in the biosynthetic pathway, phytoene, which is then desaturated, producing 11 conjugated double bonds to form lycopene, the red pigment in ripe tomato fruit (**Figure 1**). Nearly all other carotenoids can be derived from lycopene. Lycopene can be cyclized on either or both ends to form α- or β-carotene, and these in turn can be oxygenated to form xanthophylls such as β-cryptoxanthin, zeaxanthin, or lutein (**Figure 1** and **Figure 2**). Carotenoids having fewer than 40 carbons can result from loss of carbons within the chain (norcarotenoids) or loss of carbons from the end of the molecule (apocarotenoids). Longer carotenoids, homocarotenoids (C45–C50), are found in some bacterial species. The alternating double bonds along the backbone of carotenoid molecules form a polyene chain, which imparts unique qualities to this group of compounds. This alternation of single and double bonds also allows a number of geometrical isomers to exist for each carotenoid (**Figure 1**). For lycopene, the theoretical number of steric forms is 1056; however, when steric hindrance is considered, that number is reduced to 72. In nature most carotenoids are found in the all-*trans* form although mutants are known in plants, e.g., *Lycopersicon esculentum* (Mill.) var. Tangerine tomato, and eukaryotic algae that produce poly-*cis* forms of carotenoids. The mutant plant is missing an enzyme, carotenoid isomerase (CRTISO), which catalyzes the isomerization of the *cis* isomers of lycopene and its precursors to the all-*trans* form during biosynthesis. Light can also cause *cis* to *trans* isomerization of these carotenoids depending upon the surrounding environment. The isomeric form determines the shape of the molecule and can thus change the properties of the carotenoid affecting solubility and absorbability. *Trans* forms of carotenoids are more rigid and have a greater tendency to crystallize or aggregate than the *cis* forms. Therefore, *Cis* forms may be more easily absorbed and transported. End groups such as the β or ε rings of α-carotene and β-carotene and the amount of oxygenation will also affect carotenoid properties.

Chemical Properties

In general, carotenoids are hydrophobic molecules and thus are soluble only in organic solvents, having only limited solubility in water. Addition of hydroxyl groups to the end groups causes the carotenoid to become more polar, affecting its solubility in various organic solvents. Alternatively, carotenoids can solubilize in aqueous environments by prior integration into liposomes or into cyclic oligosaccharides such as cyclodextrins.

In general, carotenoid molecules are very sensitive to elevated temperatures and the presence of acid, oxygen, and light when in solution, and are subject to oxidative degradation.

Electronic Properties

What sets carotenoids apart from other molecules and gives them their electrochemical properties is the conjugated double bond system. In this alternating double and single bond system, the π-electrons are delocalized over the length of the polyene chain. This polyene chain or chromophore imparts the characteristic electronic spectra and photophysical and photochemical properties to this group of molecules. The highly delocalized π-electrons require little energy to reach an excited state so that light energy can cause a transition.

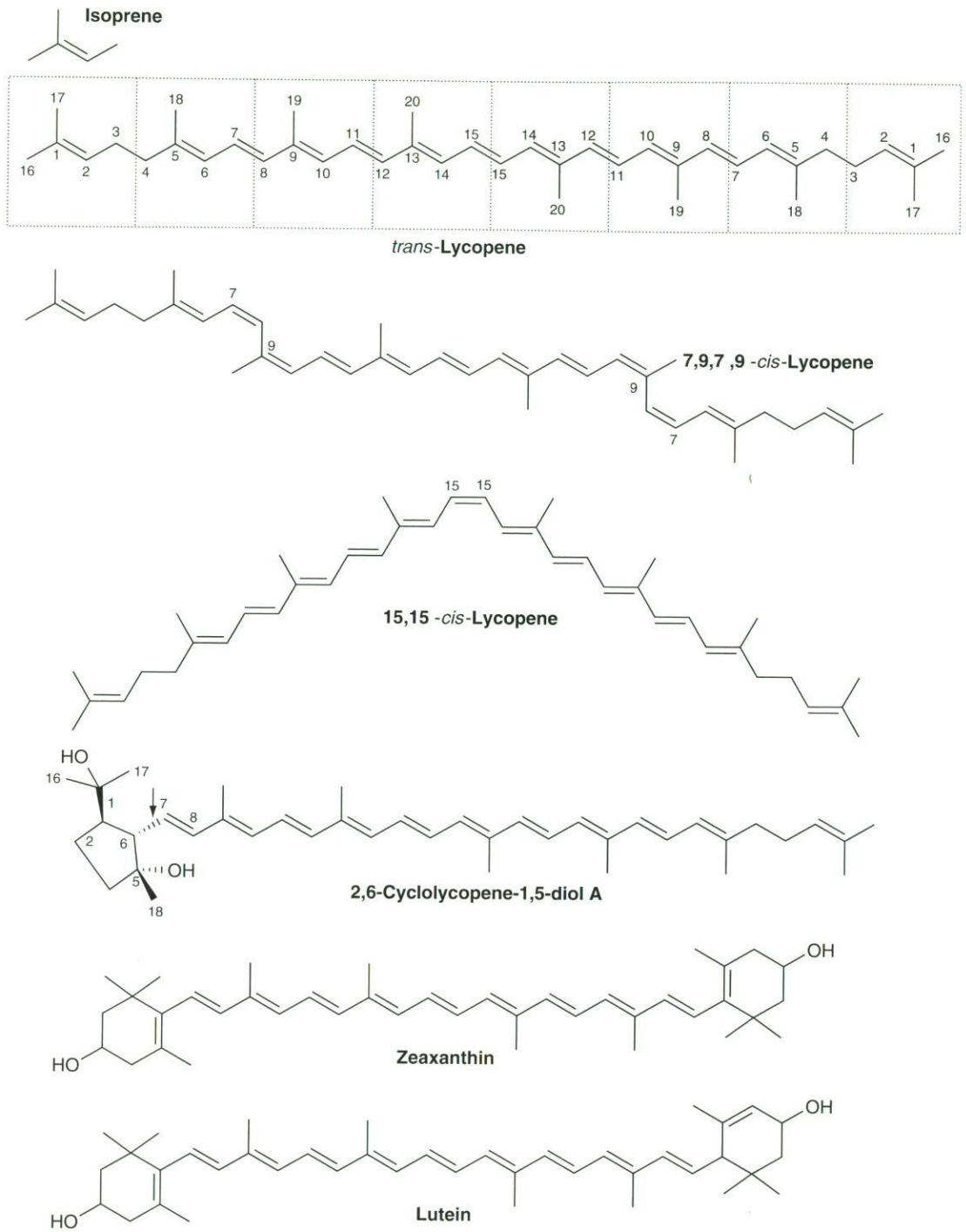

Figure 1 Carotenoid structures. Lycopene is shown with numbered carbons. The down arrow on 2,6-cyclolycopene-1,5-diol A indicates the only difference from the B isomer.

The length of the conjugated polyene or chromophore affects the amount of energy needed to excite the π-electrons. The longer the conjugated system, the easier it is to excite, so longer wavelengths of light can be absorbed. The result is that phytoene, having three conjugated double bonds is colorless, and phytofluene, having five, is colorless, but fluoresces green under UV light. Zeta-carotene has seven, absorbs light at ~400 nm and appears yellow, while neurosporene has nine, absorbs light at ~451, and appears orange, and lycopene has eleven conjugated double bonds,

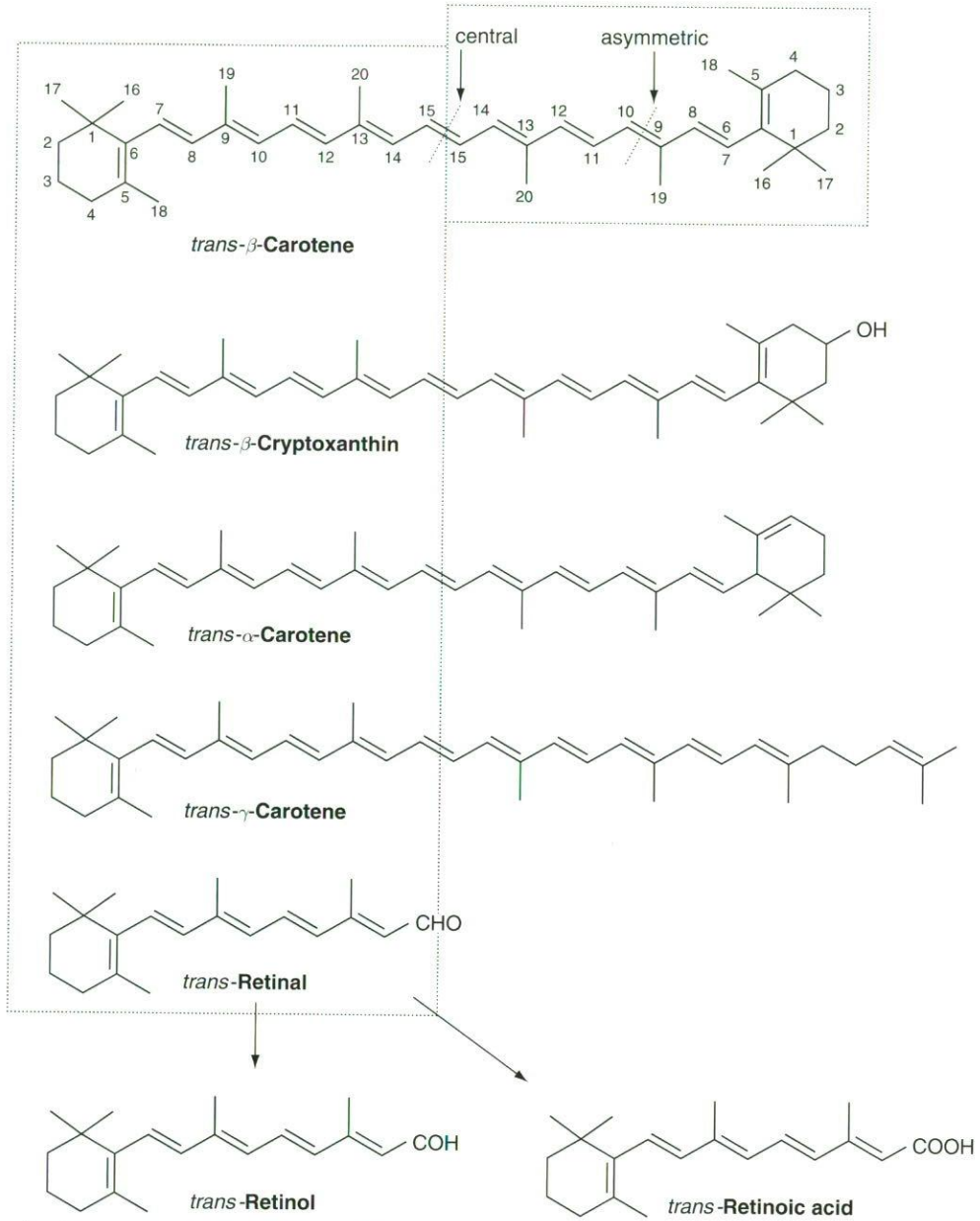

Figure 2 Provitamin A carotenoids. Dotted lines indicate the provitamin A moiety.

absorbs at ~472, and appears red. The polyene chain also allows transfer of singlet or triplet energy.

Reactions

Light and Chemical Energy

The basic energy-transfer reactions are assumed to be similar in plants and animals, even though environments differ. Excess light can cause excitation of porphyrin molecules (porphyrin triplets). These triplet-state porphyrin molecules can transfer their energy to oxygen-forming singlet oxygen, $^1O_2$. Singlet oxygen can damage DNA and cause lipid peroxidation, thereby killing the cell. Carotenoids, having nine or more conjugated double bonds, can prevent damage by singlet oxygen through: (1) transfer of triplet energy from the excited porphyrin to the carotenoid, forming a carotenoid triplet, which would be too low in energy for further transfer and would simply dissipate as heat; or (2) singlet oxygen energy could transfer to the carotenoid, also forming a triplet carotenoid, dissipating heat, and returning to the ground state. This ability to quench sensitized triplets has been useful in treating protoporphyria (PP) and

congenital erythropoietic porphyria (CEP) in humans. Porphyrias are disorders resulting from a defect in heme biosynthesis. Precursor porphyrins accumulate and can be sensitized to the singlet state and drop to the lower triplet state. The triplet state is longer-lived and thus more likely to react with other molecules such as oxygen to form singlet oxygen, which can cause cellular damage. Because β-carotene can transfer and dissipate either sensitized triplet or singlet oxygen energy it has been used to treat these disorders.

Light absorption and possibly scavenging of destructive oxygen species by the xanthophylls lutein and zeaxanthin are also important in the macula of the primate eye. Lutein and two isomers of zeaxanthin are selectively accumulated in the macula, creating a yellow area of the retina responsible for high visual acuity (smaller amounts are also found in the lens). Both carotenoids absorb light of about 450 nm 'blue light,' thus filtering light to the light receptors behind the carotenoid layer in the macula. Filtering blue light can reduce oxidative stress to retinal light receptors and chromatic aberration resulting from the refraction of blue light. A similar filter effect may occur in the lens, but the concentration of the xanthophylls is much lower, and further protection occurs with age when the lens yellows. Whether scavenging of destructive oxygen species by these carotenoids is useful here is unproven, but the retina is an area of higher blood flow and light exposure than other tissues.

Cleavage to Vitamin A

Provitamin A carotenoids are sources of vitamin A. Of the 50–60 carotenoids having provitamin A activity, β-carotene, β-cryptoxanthin, and α-carotene are the major sources of vitamin A nutrition in humans, β-carotene being the most important (**Figure 2**). Vitamin A (retinol) and its derivatives retinal and retinoic acid perform vital functions in the vertebrate body. Retinal (11-*cis* retinal) combined with opsin functions in the visual system in signal transduction of light reception. Retinol and retinoic acid function in reproduction (spermatogenesis), growth regulation (general development and limb morphogenesis), and cell differentiation. Provitamin A activity requires at least one unsubstituted β-ionone ring, the correct number and orientation of methyl groups along the polyene backbone, and the correct number of conjugated double bonds, preferably in the *trans*-isomer orientation. Two pathways for the formation of retinal from β-carotene have been proposed. First, central cleavage by which β-carotene 15,15′-mono- or dioxygenase catalyzes β-carotene cleavage to form two molecules of retinal, which can then be converted to retinol or retinoic acid (**Figure 2**). Some debate on the mechanism of the β-carotene central cleavage enzyme still exists, but evidence leans towards activity as a monooxygenase, not a dioxygenase. Alternatively, in the eccentric cleavage pathway β-carotene can be cleaved at any of the double bonds along the polyene backbone (other than the 15-15′double bond). Products of these reactions (apocarotenals) are then further metabolized to retinoic acid and retinol. An asymmetric cleavage enzyme has recently been cloned that cleaves β-carotene at the 9′-10′-double bond to form β-ionone and β-apo-10′-carotenal. The discovery of this enzyme indicates at least some eccentric cleavage occurs in vertebrates. This eccentric cleavage process has been proposed to occur during more oxidative conditions, while central cleavage would predominate under normal physiological conditions. Central cleavage is considered to be the major pathway because of the scarcity of eccentric cleavage products detected *in vivo*.

Radical Reactions

Excess amounts of radicals, molecules having unpaired electrons, e.g., peroxyls ($ROO^{\bullet}$), can be created in tissues exogenously, e.g., by light exposure, or endogenously, e.g., by overexercising. Radicals react with lipids, proteins, and DNA causing damage, which possibly contributes to disease symptoms and aging. The special properties of the polyene chain make carotenoids susceptible to electrophilic attack, resulting in formation of resonance-stabilized radicals that are less reactive.

Three possible reactions can occur with carotenoids.

1. Adduct formation ($CAR + R^{\bullet} \rightarrow R\text{-}CAR^{\bullet}$); these products should be stable because of resonance in the polyene structure. If the radical were a lipid peroxyl, this reaction ($CAR + ROO^{\bullet} \rightarrow ROO\text{-}CAR^{\bullet}$) would prevent further propagation (chain-breaking).
2. Hydrogen atom abstraction ($CAR + R^{\bullet} \rightarrow CAR^{\bullet} + RH$), where a hydrogen atom is taken from the carotenoid allylic to the polyene chain, leaving a resonance-stabilized carotenoid radical.
3. Electron transfer ($CAR + R^{\bullet} \rightarrow CAR^{\bullet +} + R^{-}$), which has been reported in plant and cyanobacterial photosystems using laser flash photolysis of Photosystem II.

In many cases, the products formed are colorless, thus revealing the bleaching effect of many oxidants on carotenoids. Further oxidation of the carotenoid or carotenoid radical can occur as in studies of soybean (*Glycine max*) and recombinant pea (*Pisum sativum*) lipoxygenase-mediated cooxidation of carotenoids

and polyunsaturated fatty acids. Approximately 50 breakdown products of β-carotene were detected. This large number of products seems to indicate a random attack along the polyene chain of β-carotene by a linoleoylperoxyl radical. Studies using potassium permanganate, a metalloporphyrin (a P450 enzyme center mimic), and autooxidation have been performed with lycopene, resulting in formation of a number of apo-lycopenals and apo-lycopenones. However, only two metabolites of lycopene have been identified in human plasma, 2,6-cyclolycopene-1,5 diols A and B (**Figure 1**). Additionally, seven metabolites of the carotenoids lutein and zeaxanthin have been detected in human tissues.

Prooxidant Behavior

The ability to quench singlet oxygen, porphyrin triplet energies, and free radical reactions are examples of the antioxidant nature of carotenoids. An *in vitro* study showed that, at low partial pressures of oxygen (pO_2), β-carotene consumed peroxy radicals efficiently as in: $CAR + ROO^{\bullet} \rightarrow CAR^{\bullet+} + ROO$. At higher pO_2, however, β-carotene became a prooxidant through autooxidation. Recently, experiments in intact murine normal and tumor thymocytes showed that β-carotene lost its antioxidant potency at higher pO_2, and the effect was more pronounced in tumor cells. It is still unclear, however, whether some effects of carotenoid behavior at higher pO_2 are due to prooxidant activity or simply lack of antioxidant ability. Prooxidant effects of β-carotene have also been used to explain results from intervention trials of β-carotene supplementation in diets of smokers or individuals suffering from asbestosis where the incidence of carcinogenesis was higher in those individuals taking the β-carotene supplement. Generation of deleterious oxidation products from β-carotene reaction with reactive oxygen species in tobacco smoke or as a result of asbestosis has been proposed. Interference with retinoid signaling was also considered. However, whether those effects were due to prooxidant behavior or lack of antioxidant ability is still unclear.

Dietary Sources

Carotenoids cannot be synthesized by humans; therefore they must be obtained from dietary sources. These are primarily highly pigmented red, orange, and yellow fruits and vegetables. The carotenoid lycopene is red; however, not all red fruits and vegetables contain lycopene. For example, the red in strawberries, apples, and cherries is a result of their anthocyanin content; whereas, tomatoes, watermelon, and pink grapefruit derive their red color from lycopene. The carotenoids β-carotene, β-cryptoxanthin, lutein, zeaxanthin, and violaxanthin are yellow to orange, and phytoene and phytofluene are colorless. Green, leafy vegetables also contain carotenoids, whose colors are masked by the green color of chlorophyll. **Table 1** lists carotenoids

Table 1 Carotenoid content (μg per g fresh weight) of fresh fruit and vegetables

Carotenoid	*Concentration (μg per g fresh weight)*	*Source*
Lycopene	380–3054	Gac (*Momordica cochinchinensis*, Spreng) aril
	179–483	Autumn olive (*Elaeagnus umbellate*)
	27–200	Tomato
	23–72	Watermelon
	53	Guava
	19–40	Papaya
	8–33	Grapefruit, pink
β-Carotene	101–770	Gac aril
	49–257	Carrot, orange
	16–216	Cantaloupe
	15–92	Kale
	0.5–92	Sweet potato
	47–89	Spinach
	46	Turnip greens
	26–64	Apricot
	22–58	Gac mesocarp
	3–70	Tomato
	42	Squash, butternut
	40	Swiss chard
	14–34	Mango
	33	Collards
	4–10	Grapefruit, pink
	0.51–1.2*	Orange (*blood)
Lutein	64–150	Kale
	6–129	Mango
	108	Parsley
	39–95	Spinach
	33–51	Collards
	15–28	Broccoli
	27	Chinese cabbage
	26	Watercress
	25	Pepper, orange
	24	Squash, butternut
	1–7	Tomato
Zeaxanthin	16–85	Pepper, orange
	43	Gou Qi Zi (*Lycium barabarum*)
	9	Gac aril
	22	Pepper, red
	7	Watercress
	1–5	Spinach
	5	Parsley
	5	Japanese persimmon
	1–3	Kale
	3	Squash, butternut
	0.4	Broccoli
	0.03–0.5	Tomato

Continued

Table 1 Continued

Carotenoid	*Concentration (μg per g fresh weight)*	*Source*
Lutein + zeaxanthin	71–3956	Kale
	119	Spinach
	84	Turnip greens
	26	Lettuce
	24	Broccoli
	21	Squash, zucchini
	16	Brussel sprouts
	8	Japanese persimmon
	7	Watercress
	6	Beans, green snap
	5	Tangerine
β-Cryptoxanthin	22	Pepper, sweet red
	14	Japanese persimmon
	11	Starfruit
	0.7–9	Pepper, chili
	2–8	Pepper, orange
	0.5–5	Tangerine
	4	Cilantro
	1.4	Papaya
	1	Watermelon
α-Carotene	20–206	Carrot
	8	Squash, butternut
	2	Collards
	1	Tomato
	0.7–0.9	Beans, green snap
	0.5	Swiss chard

found in fruits and vegetables. Smaller amounts are also available from animal sources such as ocean fish and dairy products. The pink color of salmon, for example, is derived from the xanthophylls, astaxanthin and canthaxanthin, which they obtain from eating small crustaceans and krill. Lutein imparts its yellow-orange color to eggs, and milk, butter, and cheese contain retinols and β-carotene. Carotenoids, such as lutein from marigolds and bixin (red color) from annatto, are also used widely as colorants in processed foods to make them more attractive.

Concentrations of carotenoids in fruit and vegetable sources vary, resulting from differences in conditions under which they are grown (temperature, amount of sunlight, degrees of stress from extremes in climate such as drought, heat, and cold), genotype, and maturity or ripeness. The carotenoid content in animal sources depends upon amounts contained in animal feeds and seasons of the year, which affect the availability of carotenoid-containing plants eaten by grazing animals.

Human diets and tissues contain six carotenoids in significant amounts (listed in **Table 1**). Lycopene is typically the carotenoid consumed in greatest amounts in Western diets. Per capita intakes in Europe and North America average from 1.6 to more than 18 mg lycopene per day. More than 85% of the lycopene in North American diets comes from tomato products, which also contain significant amounts of other carotenoids (α- and β-carotene and lutein/zeaxanthin), as well as vitamins C, A, and E, and potassium and folic acid. (Flavonoids are also found in tomato skin; thus, cherry tomatoes contain higher concentrations.) In the US, the annual per capita consumption of tomatoes by 1999 averaged about 17.6 pounds of fresh and 72.8 pounds of processed tomatoes.

Effects of Storage and Processing

Carotenoids are susceptible to oxidative degradation and isomerization resulting from storage and processing conditions. These reactions result in both loss of color and biological activity and formation of often unpleasant volatile compounds. Degradation occurs upon exposure to oxygen and is accelerated by the presence of substances such as metals, enzymes, unsaturated lipids, and prooxidants; exposure to light; and conditions that destroy cell wall and ultrastructural integrity. Heating can promote isomerization of the naturally occurring all-*trans* to various *cis* isomers. This process then affects bioavailability of the carotenoid. Processing also affects bioavailability by macerating tissues, destroying or weakening cell ultrastructure, denaturing or weakening complexes with proteins, and cleaving ester linkages, thereby releasing carotenoids from the food matrix.

Processed foods are frequently fortified with carotenoids to increase nutritive value and/or enhance attractiveness. For example, annatto, an extract from the seeds of the *Bixa orella* tree, containing the carotenoids bixin and norbixin, is added to butter, margarine, and processed cheese to give a yellow-orange color to these products. Tomato oleoresin is added to processed tomato products, increasing lycopene content while enhancing their attractive red color.

Physiology

Digestion

Numerous factors affect the intestinal absorption of carotenoids. Digestion of food in the stomach increases accessibility of carotenoids for absorption by maceration in HCl and digestive enzymes. The acidic environment of the stomach helps to disrupt cell walls and other cellular ultrastructure of raw fruits and vegetables and causes further breakdown of cooked foods to release carotenoids from food matrices in which they are contained or bound.

Carotenoids in green leafy vegetables are found in chloroplasts; those in fruit are located in chromoplasts. Absorption studies comparing plasma levels of β-carotene and retinol after consuming fruit vs. green leafy vegetables showed that β-carotene is more efficiently absorbed from fruit, indicating that chloroplasts (or the bonds linking chloroplast proteins and carotenoids) are more resistant to disruption in the digestive tract than chromoplasts. Thus, the location of a carotenoid in the cell affects its accessibility.

Carotenoid isomerization can occur in the acidic gastric milieu. Lycopene present in fruits and vegetables occurs almost exclusively as the all-*trans* isomer, but is converted to *cis* isomers, which seem to be more bioavailable. Plasma and tissue profiles show that *cis* isomers make up more than 50% of the total lycopene present. On the other hand, studies show that no *trans/cis* isomerization of β-carotene occurs in the stomach. In fact, evidence has been found for transfer of a significant portion of both β- and α-carotene to the fat phase of the meal in the stomach, which would increase bioavailability of these carotenoids for absorption. No studies are available relating isomerization to bioavailability of other carotenoids.

Absorption and Transport

Because carotenoids are hydrophobic molecules, they are associated with lipophilic sites in cells, such as bilayer membranes. Polar substituents such as hydroxyl groups decrease their hydrophobicity and their orientation with respect to membranes. Lycopene and β-carotene are aligned parallel to membrane surfaces to maintain a hydrophobic environment, whereas the more polar xanthophylls lutein and zeaxanthin become oriented perpendicular to membrane surfaces to keep their hydroxyl groups in a more hydrophilic environment. These differences can affect the physical nature of a membrane as well as its function. Carotenoids can form complexes with proteins, which would aid them in moving through an aqueous environment. They can also interact with hydrophobic regions of lipoproteins. Carotenoproteins have been found mainly in plants and invertebrates, but intracellular β-carotene-binding proteins have been found in bovine liver and intestine and in livers of the rat and ferret. In addition, a xanthophyll-binding protein has been found in human retina and macula. Carotenoids are also present in nature as crystalline aggregates (lycopene in chromoplasts) or as fine dispersions in aqueous media (β-carotene in oranges).

In the intestinal lumen (**Figure 3**) where carotenoids are released from the food matrix, cleavage of carotenoproteins and fatty acid esters by carboxylic ester hydrolase, which is secreted by the pancreas, can occur. Carotenoids are then solubilized into lipid micelles. These hydrophobic compounds are thus more efficiently absorbed when accompanied by at least a small amount of fat. The amount of fat for optimal carotenoid absorption seems to differ among carotenoids. For example, lutein esters require more fat for optimal absorption than β-carotene. These differences have not been quantified for each carotenoid. In addition, the presence of a nonabsorbable, fat-soluble component was shown to

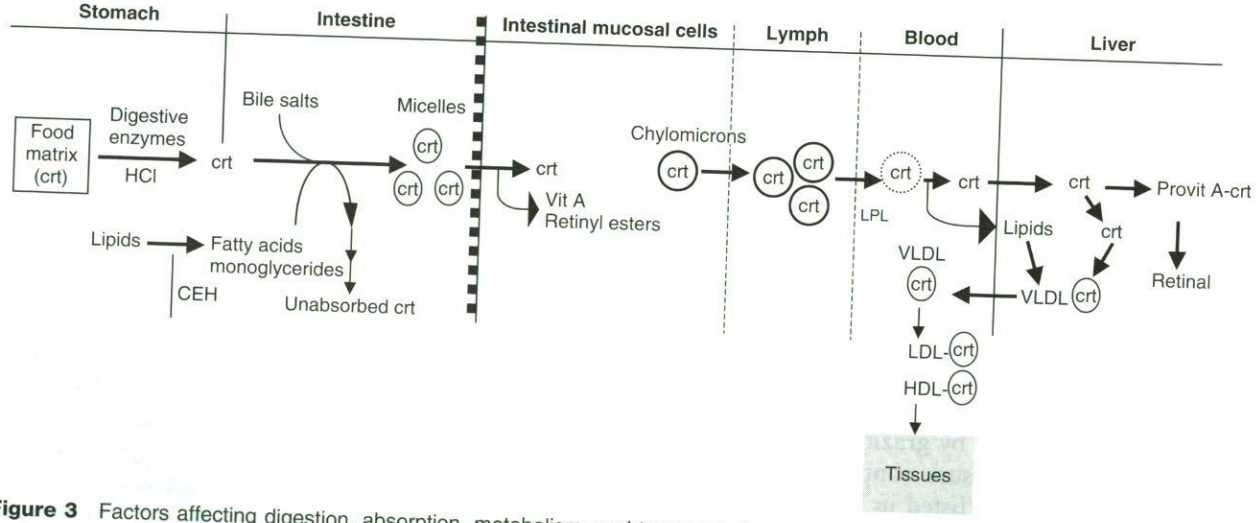

Figure 3 Factors affecting digestion, absorption, metabolism, and transport of carotenoids. crt, carotenoids; CEH, carboxylic ester hydrolase, secreted by the pancreas; LPL, lipoprotein lipase; VLDL, very low-density lipoprotein; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

decrease carotenoid absorption. Sucrose polyester, a nonabsorbable fat replacer decreased carotenoid levels in plasma after ingestion by 20–120%. The extent of this inhibition depends upon the amount of nonabsorbable compound ingested, as well as the particular carotenoid under consideration. The mechanism for this inhibition is apparently similar to the action of fiber, i.e., sequestration. The type of fat that is ingested along with carotenoids will also affect carotenoid absorption. As macerated food passes into the intestinal lumen, carotenoids freed from the food matrix then become incorporated into micelles, consisting of free fatty acids, monoglycerides, phospholipids, and bile acids. Many other factors can affect intestinal absorption such as micelle size, phospholipid composition, solubilization of carotenoids into mixed micelles, and concentration of available bile salts, among others.

The presence of other carotenoids can affect the absorption of carotenoids into intestinal mucosal cells, since carotenoids can compete for absorption or facilitate the absorption of another. Data on carotenoid interactions are not clear. Human studies show that β-carotene decreases lutein absorption, while lutein has either no effect or a lowering effect on β-carotene absorption. Although not confirmed in humans, the inhibitory effect of lutein on β-carotene absorption might be partly attributed to the inhibition of the β-carotene cleavage enzyme by lutein shown in rats. Beta-carotene also seemed to lower absorption of canthaxanthin, whereas canthaxanthin did not inhibit β-carotene absorption. Studies showed that β-carotene increased lycopene absorption, although lycopene had no effect on β-carotene. Alpha-carotene and cryptoxanthin show high serum responses to dietary intake compared to lutein. In addition, *cis* isomers of lycopene seem to be more bioavailable than the all-*trans*, and selective intestinal absorption of all-*trans* β-carotene occurs, as well as conversion of the 9-*cis* isomer to all-*trans* β-carotene. It is clear, then, that selective absorption of carotenoids takes place into the intestinal mucosal cell.

Another complicating factor in the intestinal mucosal cell is the partial conversion of provitamin A carotenoids (β- and α-carotenes and cryptoxanthin) to vitamin A (primarily to retinyl esters). Therefore, in absorption studies these metabolic reactions must be accounted for in measuring intestinal transport. Nonprovitamin A carotenoids such as lycopene, lutein, and zeaxanthin are incorporated intact, although some cleavage can occur. Earlier studies on rats indicated that lycopene and β-carotene are absorbed by passive diffusion. However, recent evidence from the kinetics of β-carotene transport through Caco-2 cell monolayers indicates the involvement of a specific epithelial transporter that facilitates absorption.

In the intestinal mucosa, both carotenoids and retinyl esters are incorporated into chylomicrons and secreted into the lymph for transport to blood. In blood, lipoprotein lipase rapidly degrades the chylomicrons, and the liver sequesters the resulting carotenoid-containing fragments. The liver then secretes carotenoids back into the bloodstream in association with hepatic very low-density lipoproteins (VLDL). Most carotenoids in fasting plasma are carried by low-density lipoproteins (LDL) and high-density lipoproteins (HDL). Seventy-five per cent of the hydrocarbon carotenoids, e.g., lycopene and β-carotene, are associated with LDL, the rest is associated with HDL and, in smaller amounts, with VLDL. More polar carotenoids such as lutein and zeaxanthin are found equally distributed between HDL and LDL. After ingestion, carotenoids first appear in the bloodstream in chylomicrons, resulting from excretion from intestinal mucosal cells (4–8 h). HDL carotenoid levels peak in the circulation between 16 and 28 h; LDL carotenoid levels peak between 24 and 48 h. The bloodstream then transports carotenoids to different tissues (e.g., liver, prostate gland, fat, ocular macula) where they are sequestered by various mechanisms.

Distribution and Impact on Health

In general, carotenoid concentrations in serum reflect concentrations contained in the food that is ingested. Carotenoids have been found in various human organs and tissues. These include human liver, lung, breast, cervix, skin, and adipose and ocular tissues. The major storage organs are adipose tissue (probably because of its volume) and the liver. Tissues containing large amounts of LDL receptors seem to accumulate high levels of carotenoids, probably as a result of nonspecific uptake by lipoprotein carriers. Preferential uptake, however, is indicated in some cases. For example, unusually high concentrations of phytoene in the lung, ζ-carotene and phytofluene in breast tissue, lycopene in the prostate and colon, lycopene, β-carotene, and phytofluene in cervical tissue, and lutein and zeaxanthin in ocular tissues have been found.

The epidemiological findings that the ingestion of tomato and tomato products is strongly correlated with a reduced risk of several types of cancer, particularly prostate cancer, has stimulated a great deal of research on the protective effects of lycopene. Lycopene is the most efficient biological antioxidant. Hence, it has been assumed that it is this antioxidant activity that is responsible for the protection

against prostate cancer. However, a recent study in which carcinogenesis was induced in rats using *N*-methyl-*N*-nitrosourea showed that a diet containing whole tomato powder inhibited development of prostate cancer, but the same diet to which pure synthetic lycopene was added instead did not. These results indicate that lycopene alone was ineffective in reducing the incidence of prostate cancer. Therefore, either some other element in the tomato powder was the effective agent or the effect was obtained by lycopene working in concert with other tomato constituents. Obviously, more studies are required to determine which elements contained in tomato are responsible for the protective effect.

The finding that lutein and zeaxanthin are accumulated in the macula lutea of the eye has led to the hope that dietary supplementation might reduce the risk of age-related macular degeneration (AMD), which affects the central portion of the retina and is the most common cause of irreversible blindness in the Western world. Some studies have indicated benefits of diets supplemented with lutein and zeaxanthin from spinach in preventing AMD; others found no significant correlation between plasma levels of these carotenoids and reduced risk of AMD. Lutein, zeaxanthin, and a zeaxanthin stereoisomer 3R, 3′S(=meso)-zeaxanthin form the yellow pigment of the macula lutea. 3R, 3′S(=meso)-zeaxanthin is not found in either food or plasma in significant amounts. Also notable is that, in most food consumed in large quantities, the concentration of lutein is much greater than that of zeaxanthin (e.g., see **Table 1**, spinach, kale, broccoli, tomato). The yellow pigment of the macula is located in the center of the macula, covering the central fovea and overlapping the avascular zone. This location would allow the pigment to shield the photoreceptors from blue light. An environmental factor that seems to play a role in the development of age-related macular degeneration is ocular exposure to sunlight, in particular a history of exposure to blue light in the preceding 20 years. Light has been shown to induce oxidative damage in the presence of photosensitizers. Macular carotenoids are distributed in a pattern that is particularly advantageous. The two stereoisomers of zeaxanthin are concentrated in the central area and lutein in higher concentrations in the more peripheral regions. The lutein: zeaxanthin ratio in the center of the macula is about 0.8, in the peripheral regions about 2.4, but in plasma between 4 and 7. Therefore, the macula is able to concentrate lutein and zeaxanthin, change concentration ratios that are normally found in plasma, and invert the ratio to achieve higher zeaxanthin concentrations in the center of the macula lutea. The exact mechanism for this accumulation is not known; however, a specific membrane-associated, xanthophyll-binding protein was recently isolated from the human retina.

Carotenoids are believed to play a significant role in protecting skin from oxidative damage. *In vivo* measurements in humans of lycopene, β-, ζ-, γ-, and α-carotenes, lutein and zeaxanthin, phytoene, and phytofluene have shown that carotenoid concentrations are correlated with the presence or absence of skin cancer and precancerous lesions. Carotenoids are also believed to protect against several other types of cancer, cardiovascular diseases, and cataract formation and aid in immune function and gap-junction communication between cells, which is believed to be a protective mechanism related to their cancer-preventative activities.

Conclusions

Numerous studies indicate that carotenoids and their metabolites play a role in combating degradative reactions that are harmful to human health. Most of these functions seem to be related to their antioxidant nature and ability to dissipate energy from light and free radical-generating reactions. Obviously much research is still required to shed light onto mechanisms involved in these protective functions. Other fascinating roles in nature are also being discovered, for example, the signaling of apparent good health and consequently good potential parenting in birds by the red coloration of beaks, which seems to serve as an attractant to prospective mates.

See also: **Carotenoids**: Epidemiology of Health Effects. **Vitamin A**: Biochemistry and Physiological Role.

Further Reading

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